

Practitioner's Docket No. U 013571-6

PATENT

**TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE (DO/US)--
ENTRY INTO THE U.S. NATIONAL STAGE UNDER CHAPTER I**

PCT/RU00/00477 22 November 2000 08 December 1999 & 23 June 2000

INTERNATIONAL APPLICATION NO. INTERNATIONAL FILING DATE PRIORITY DATE CLAIMED
**USE OF POLYACRYLAMIDE GEL FOR FORMING A CAPSULE IN THE TISSUE OF THE
ORGANISM OF A MAMMAL, A METHOD OF CULTIVATING CELLS, AND A METHOD OF
TREATING ONCOLOGICAL DISEASES AND DIABETES MELLITUS**

TITLE OF INVENTION

Dmitry Vladimirovich ZYBIN, Alexei Gennadievich KOTELEVITS, Sergei Evgenievich SEVERIN
Vladimir Konstantinovich SOLOGUB, Ljubov Leonidovna MIRONOVA

APPLICANT(S)

Box PCT

Optional Customer No. Bar Code

Assistant Commissioner for Patents

Washington D.C. 20231

ATTENTION: DO/US



00140

PATENT TRADEMARK OFFICE

NOTE: *The completion of those filing requirements that can be made at a time later than 20 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 U.S.C. 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. 1.491, which states: "An international application enters the national stage when the applicant has filed the documents and fees required by 35 U.S.C. 371(c) within the periods set forth in § 1.494 and § 1.495."*

WARNING: *Where the items are those that can be submitted to complete the entry of the international application into the national phase subsequent to 20 months from the priority date, the application is still considered to be in the international stage. And if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. 1.10 must be used (because international application papers are not covered by an ordinary certificate of mailing. 37 C.F.R. 1.8(2)(xi)).*

NOTE: *Documents and fees must be clearly identified as a submission to enter the national stage under 35 U.S.C. 371, otherwise the submission will be considered as being made under 35 U.S.C. 111. 37 C.F.R. 1.494(f).*

CERTIFICATION UNDER 37 C.F.R. 1.10*

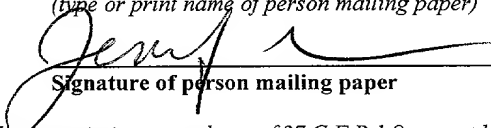
*(Express Mail label number is **mandatory**.)*

(Express Mail certification is optional.)

I hereby certify that this paper, along with any document referred to, is being deposited with the United States Postal Service on this date July 31, 2001, in an envelope as Express Mail Post Office to Addressee, "mailing Label Number EL728214230US", addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

JENNIFER RASHKIN

(type or print name of person mailing paper)


Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*

*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

- a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).
- b. ☒ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. 1.492), as indicated below:

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
*	TOTAL CLAIMS	11--20=		x\$ 18.00=	\$
	INDEPENDENT CLAIMS	3--3=		x\$ 80.00=	
	MULTIPLE DEPENDENT CLAIMS(S) (if applicable) + \$270.00				
BASIC FEE**	<p>The international search fee, as set forth in § 1.445(a)(2) to be paid to the US PTO acting as an international Searching Authority:</p> <p><input type="checkbox"/> has been paid (37 CFR 1.492(a)(2)).....\$710.00</p> <p><input checked="" type="checkbox"/> has not been paid (37 CFR 1.492(a)(3)).....\$1,000.00</p> <p><input type="checkbox"/> where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5))..... \$860.00</p>				
	Total of above Calculations				=1,000.00
	Reduction by ½ for filing by small entity, if applicable. Statement may also be filed. (note 37 CFR 1.9, 1.27, 1.28)				-500.00
	Subtotal				\$500.00
	Total National Fee				\$500.00
	Fee for recording the enclosed assignment document \$40.00 (37 CFR 1.21(h)). (See Item 10 below). See attached "ASSIGNMENT COVER SHEET (37 CFR 3.34)".				
TOTAL	Total Fees enclosed				\$500.00

****WARNING:** *"To avoid abandonment of the application, the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 20 months from the priority date; *** (2) the basic national fee (see § 1.492(a)). The 20-month time limit may not be extended." 37 C.F.R. § 1.494(b).*

- i. ☒ A check in the amount of \$ 500.00 to cover the above fees is enclosed.
ii. ☐ Please charge Account No. _____ in the amount of \$ _____.

A duplicate copy of this sheet is enclosed.

WARNING: *If the translations of the international application, oath or declaration and national fee have not been submitted by the applicant within twenty (20) months from the priority date, the applicant will be so notified and given a period of time within which to file the translation and/or oath or declaration in order to prevent abandonment. The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than twenty (20) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than twenty (20) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 will apply. 37 CAR § 1.494(c); Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35.*

3. A copy of the International application as filed (35 U.S.C. 371(c)(2)):
- a. ☒ is transmitted herewith.
 - b. ☐ is not required, as the application was filed with the United States Receiving Office.
 - c. ☐ has been transmitted
 - i. ☐ by the International Bureau. Date of mailing of the application from form PCT/IB/308): _____.
 - ii. ☐ by applicant on _____.
Date

NOTE: *Section 1.494(b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 20 months from the priority date to avoid abandonment. "The International Bureau nominally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies the applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage and applicant has received notice from the International Bureau, applicant need only pay the basic national fee by 20 months from the priority date." [This can now be paid subsequently with a surcharge.] Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35.*

4. A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
- a. ☒ is transmitted herewith.
 - b. ☐ is not required as the application was filed in English.
 - c. ☐ was previously transmitted by applicant on _____.
Date

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: The Notice of January 7, 1993 indicates that 37 C.F.R. § 1.494(d) was "amended to clarify the existing practice that PCT Article 19 Amendments must be submitted by 20 months from the priority date, which time may not be extended." This Notice further advises: "Of course, the failure to do so does not result in loss of the subject matter of PCT Article 19 amendments. The applicant may submit that subject matter in a preliminary amendment filed under Section 1.121. In many cases, filing an amendment under Section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 35. See item 11(c) below.

- a. ☐ are transmitted herewith.
- b. ☐ have been transmitted
 - i. ☐ by the International Bureau. Date of mailing of the amendment (from form PCT/IB/308): _____.
 - ii. ☐ by applicant on _____
Date
- c. ☒ have not been transmitted, as
 - i. ☐ no notification has been received that the International Search Authority has received the Search Copy.
 - ii. ☐ the Search Copy was received by the International Searching Authority, but the Search Report has not yet been issued. Date of receipt of Search Copy from form PCT/ISA/202) _____.
 - iii. ☒ applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210): February 22, 2001
 - iv. ☐ the time limit for the submission of amendments has not yet expired. The amendments, or a statement that amendments have not been made, will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)):

- a. ☐ is transmitted herewith.
- b. ☐ is not required as the amendments were made in the English language.
- c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115

- a. ☐ was previously submitted by applicant on _____
Date
- b. ☒ is submitted herewith, and such oath or declaration
 - i. ☐ is attached to the application.
 - ii. ☒ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or (c) and 5(b); and states that they were reviewed by the inventor, as required by 37 C.F.R. 1.70.
 - iii. ☐ will follow.

09/890496

II. Other document(s) or information included:

8. ☒ An international Search Report or Declaration under PCT Article 17(2)(a):
- ☒ is transmitted herewith.
 - ☐ has been transmitted by the International Bureau. Date of mailing from form PCT/IB/308): _____.
 - ☐ is not required, as the application was searched by the United States International Searching Authority.
 - ☐ will be transmitted promptly upon request.
 - ☐ has been submitted by applicant on _____.
Date
 - ☐ is not transmitted, as the international search has not yet issued.
9. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
- ☐ is transmitted herewith.
Also transmitted herewith is (are)
☐ Form PTO-1449 (PTO/SB/08A and 08B)
☐ Copies of citations listed
 - ☒ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
 - ☐ was previously submitted by applicant on _____.
Date
10. ☒ An assignment document is transmitted herewith for recording. A separate
- ☒ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or
- ☐ FORM PTO—1595
is also attached.
- ☒ Please mail the recorded assignment document to:
 - ☒ the person whose signature and address appears below.
 - ☐ the following:
11. ☒ Additional documents
- ☒ Copy of request (PCT/RO/101)
 - ☒ International Publication No. WO 01/41809
 - ☐ Specification, claims and drawing
 - ☒ Front page only
 - ☐ Preliminary amendment (37 C.F.R. § 1.121)
 - ☒ Other PCT/IB/304; One Sheet of Formal Drawings;
Certified Copy RU Appln. No. 99125349 & English Translation
Certified Copy RU Appln. No.: 2000116208 & English Translation
12. ☒ The above checked items are being transmitted
- ☐ before the 18th month publication.
 - ☒ after publication and the article 20 communication, but before 20 months from the priority date.
 - ☐ after 20 months (revival).

NOTE: Petition to revive (37 C.F.R. 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements are submitted after 20 months.

13. ☐ Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____ namely:
Date _____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 CFR 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 CFR 1.26(a).

- ☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425.

- ☒ 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: Because failure to pay the national fee within 20 months without extension (37 C.F.R. § 1.494(b)(2)), results in abandonment of the application, it would be best to always check the above box.

- ☐ 37 C.F.R. 1.492(b), (c), and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment, prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

- ☒ 37 C.F.R. 1.17 (application processing fees)
☒ 37 CFR 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).

- ☒ 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b)).

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. 1.311(b).

NOTE: 37 C.F.R. 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying or at the time of paying . . . issue fee...." From the wording of 37 C.F.R. 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

09/890496
31 JUL 2001

- ☐ 37 C.F.R. 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 20 months after the priority date.

Reg. No. 25,858

Tel. No.: (212) 708-1930

Customer No.:


SIGNATURE OF PRACTITIONER

William R. Evans

(type or print name of practitioner)

P.O. Address

c/o Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

09/890496

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Use of Polyamide Gel for Forming a Capsule in the
 Tissue of the Organism of a Mammal, a Method of Cul-
 tivating Cells, and a Method of Treating Oncological
 Diseases and Diabe- Group No.:
 tes Mellitus Examiner:
 Filed:
 For:

[] *Patent No.:

Issue Date:

*NOTE: Insert name(s) of inventor(s) and title also for patent Where statement is with respect to a maintenance fee payment,
 also insert application number and filing date, and add Box M. Fee to address.

STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(c-f) and 1.27(b-d))

With respect to the invention described in

☒ the specification filed herewith.

[] application no. _____, filed _____.

[] patent no. _____ issued _____.

I. IDENTIFICATION AND RIGHTS AS A SMALL ENTITY

I hereby state that I am

(complete either (a), (b), (c) or (d) below)

(a) Independent Inventor

☒ a below named independent inventor, and that I qualify as an independent
 inventor, as defined in 37 CFR 1.9(c), for purposes of paying reduced fees
 under Sections 41(a) and (b) of Title 35, United States Code, to the Patent and
 Trademark Office.

(b) Noninventor Supporting a Claim by Another

[] making this statement to support a claim by

for a small entity status for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35,
 United States Code. I hereby state that I would qualify as an independent inventor as defined in 37 CFR
 1.9(c) for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code,
 if I had made the above identified invention.

(c) Small Business Concern

[] the owner of the small business concern identified below:

[] an official of the small business concern empowered to act on behalf of the concern
 identified below:

Name of Concern _____

Address of Concern _____

and

that the above identified small business concern qualifies as a small business concern, as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

(d) Non-Profit Organization

☐ an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization _____

Address of Organization _____

TYPE OF ORGANIZATION

☐ University or Other Institution of Higher Education

☐ Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3))

☐ Nonprofit Scientific or Educational Under Statute of State of the United States of America

(Name of State _____)

(Citation of Statute _____)

☐ Would Qualify as Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3)), if Located in the United States of America

☐ Would Qualify as Nonprofit Scientific or Educational Under Statute of State of the United States of America, if Located in the United States of America

(Name of State _____)

(Citation of Statute _____)

and that the nonprofit organization identified above qualifies as a nonprofit organization, as defined in 37 CFR 1.9(e), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code.

II. OWNERSHIP OF INVENTION BY DECLARANT

I hereby state that rights under contract or law remain with and/or have been conveyed to the above identified

☐ person
(item (a) or (b) above)

☐ concern
(item (c) above)

☐ organization
(item (d) above)

EXCEPT, that if the rights held are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held (1) by any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, (2) any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or (3) a nonprofit organization under 37 CFR 1.9(e).

- ☐ no such person, concern, or organization
☐ person, concerns or organizations listed below*

*NOTE: Separate statements are required from each named person, concern or organization having rights to the invention as to their status as small entities. (37 CFR 1.27)

Full Name _____

Address _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

Full Name _____

Address _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

III. ACKNOWLEDGEMENT OF DUTY TO NOTIFY PTO OF STATUS CHANGE

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

IV. DECLARATION

(check the following item, if desired)

NOTE: The following verification statement need not be made in accordance with the rules published on October 10, 1997, 62 Fed. Reg. 52131, effective December 1, 1997.

NOTE: "The presentation to the Office (whether by signing, filing, submitting, or later advocating) of any paper by a party, whether a practitioner or non-practitioner, constitutes a certification under § 10.18(b) of this chapter. Violations of § 10.18(b)(2) of this chapter by a party, whether a practitioner or non-practitioner, may result in the imposition of sanctions under § 10.18(c) of this chapter. Any practitioner violating § 10.18(b) may also be subject to disciplinary action. See §§ 10.18(d) and 10.23(c)(15)." 37 CFR 1.4(d)(2).

- ☐ I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

V. SIGNATURES

(complete only (e) or (f) below)

(e)

NOTE: All inventors must sign the statement.

1. Dmitry Vladimirovich ZYBIN

Name of Inventor

Дмитрий Владимирович Зыбин Date: July 23, 2001
Signature of Inventor

2. Alexei Gennadievich KOTELEVITS

Name of Inventor

Алексей Геннадьевич Котелевич Date: July 23, 2001
Signature of Inventor

3. Sergei Evgenievich SEVERIN

Name of Inventor

Сергей Евгеньевич Северин Date: July 23, 2001
Signature of Inventor

(add lines for any additional inventors who must sign)

or

(f)

NOTE: The title of the person signing on behalf of a concern or nonprofit organization should be specified.

Name of Person Signing _____

Title of Person _____
(if signing on behalf of a concern or non-profit organization)

Address of Person Signing _____

SIGNATURE _____

DATE _____

V. SIGNATURES

(complete only (e) or (f) below)

(e)

NOTE: All inventors must sign the statement.

4. Vladimir Konstantinovich SOLOGUB

Name of Inventor

Владимир Константинович Сологуб
Signature of Inventor

Date: July 23, 2001

5. Ljubov Leonidovna MIRONOVA

Name of Inventor

Любовь Леонидовна МIRONOVA
Signature of Inventor

Date: July 23, 2001

Name of Inventor

Signature of Inventor

Date: _____

(add lines for any additional inventors who must sign)

OR

(f)

NOTE: The title of the person signing on behalf of a concern or nonprofit organization should be specified.

Name of Person Signing _____

Title of Person _____

(if signing on behalf of a concern or non-profit organization)

Address of Person Signing _____

SIGNATURE _____

DATE _____

**USE OF POLYACRYLAMIDE GEL FOR FORMING A CAPSULE
IN THE TISSUE OF THE ORGANISM OF A MAMMAL, A METHOD
OF CULTIVATING CELLS, AND A METHOD OF TREATING
ONCOLOGICAL DISEASES AND DIABETES MELLITUS**

5 The present invention relates to medicine, particularly to immunology and immunooncology, and also to the treatment of diabetes mellitus, predominantly of insulin-dependent diabetes mellitus. More particularly, the invention relates to the problem of vaccination against tumor cells and of vaccinothrapy of oncological diseases and to a new method of treating diabetes mellitus. Furthermore, the invention proposes a special
10 capsule for use in methods of treating, owing to which the treatment proves to be substantially more effective.

It is known that the problem of transplanting organs, tissues, cell cultures of mammals involves difficulties associated with the possibility of xenogenous tissue-and-cell agents to "take root" in the recipients' organism. The existing methods of transplanting
15 allo-, hetero- and xenotransplants require either powerful immunosuppressive therapy of the recipient or original procedures. These latter comprise methods of transplanting cells of various organs of human and animal fetuses, i.e., the effect of undeveloped species specificity is employed. In such a manner, e.g., islet cell cultures of the pancreas of 24—26 weeks' human fetuses are transplanted into the parenchyma of the liver or into the portal
20 vein in experiments with rats.

The place of introducing cells may be splenic pulp or muscles of the anterior abdominal wall. Cases of treating humans suffering from diabetes mellitus by a similar method are known (Skaletskii N.N., "The Effect of Cultivating Islet Cells of the Pancreas on Their Survival in the Organism of a Xenogenous Recipient", in: All-Russian
25 Conference on Transplantation of Organs, 1995, pp. 219—220 (in Russian)).

The transplantation of Leydig's cells into testicular tissue to males for treating infertility is of interest, because the rejection reaction does not occur due to the presence of a hematotesticular barrier (Zybin D.V., "Method of Treating Patients with Dysfunction of Male Sexual Sphere by Transplantation Techniques", RF Patent 2026643 of 20.01.95).

30 As a result of both above-described methods, good results were obtained in preserving the viability and activity of transplanted cells. However, the first method makes it possible to use only embryonal cells, this, for obvious reasons, involving a number of difficulties; the second method of cell therapy proves to be applicable only to male individuals.

TOP SECRET 96405560

There is known a method of vaccination and vaccinothrapy of tumors with the help of live cells. The employed cells are hybridomas or transformed cells, allogenic or autogenic. A disadvantage of such cells is their short-time existence in the organism and, correspondingly, a low immunizing effect (B.E. Souberbielle, M. Westby, S. Ganz, and J.

5 Kayaga, Comparison of four strategies for tumor vaccination in the B-16

F 10 melanoma model. *Gene Therapy* 1998, 1447—1454).

Known in the art is a method of transplantation of pancreatic islets (PIs) using microencapsulation.

The method consists in introducing (allo- or xenogenic) PIs encapsulated in spheres
10 of an alginate gel. The spheres are implanted intraperitoneally. The implantation of spheres completely replaces insulin therapy during 175 days, but in this case immunosuppressive therapy is concurrently used. Bovine PIs are administered to rats with induced diabetes without immunosuppression. Normoglycemia is maintained from several weeks to one month.

15 A certain inconvenience of the method is the necessity of using immunosuppressive therapy. Definite difficulties are involved in preparing capsules in vitro (Lanza R.P., Esker D.M., and Marsh J.P., Transplantation of islets using microencapsulation studies in diabetic rodents and dogs. *J. Mol. Med.*, 1999 Jan. 77(1): 206—10).

20 Also known is a method of vaccination and vaccinothrapy of tumors with the help of live cells. It consists in producing hybridomas of tumor cells and allogenic dendritic cells (or macrophages). The obtained hybridomas are used as vaccine preparations.

However, this method also features a low immunizing effect, caused by the short-time existence of the introduced cells in the recipient's organism (Gajewsky T.F. and Fallarino F., Rational development of tumor antigen-specific immunization in melanoma.

25 *Therapeutic Immunology*, 1997, 2, 211—225).

Therefore, the problem of increasing the life-span of transplanted cells and, as a consequence, of enhancing the immunizing effect, as well as obviating immunosuppressive therapy is now as before topical in this field of the art.

30 Specialists are aware that the problem of treating diabetes mellitus is also closely connected with the positive solution of the question of transplanting cells, whose successful solution will in many respects make for the desired effectiveness of the method of treating.

For instance, a method of treating diabetes mellitus is known, according to which implantation of cells of benignant human insulinoma is carried out, the material containing pancreatic β -cells is implanted into the musculus rectus abdominis (RF Patent 2004247).

However, problems which arise in connection with combating the predominance of the growth of fibroblasts when using a culture of β -cells for transplantation, and the necessity of precise control of the insulin production by a particular fraction of the insulinoma cell culture, called for due to the fact that tumor cells whose functional activity may vary substantially are used as the implant, offer a hindrance to the wide use of the method.

Also known is a method of treating diabetes mellitus by transplanting material containing pancreatic β -cells (RF Patent 2135193). The method of treating diabetes mellitus, predominantly insulin-dependent one, is carried out using material containing pancreatic β -cells of mammals, produced with the use of the β -cells migration phenomenon.

The material containing pancreatic β -cells is transplanted into different organs and tissues; intramuscularly, into the musculus rectus abdominis, into the liver (into the parenchyma or via the portal vein), into the splenic pulp, into the spleen artery, into the abdominal cavity, into the greater omentum, into a specially created muscular pocket.

The short period of time during which β -cells produce an insulin donor in the recipient's organism because of the effect of rejection of heterogeneous cells necessitates considerable immunosuppressive therapy.

Figure 1 illustrates the dynamics of testosterone in the blood serum of Vistar-line rats to which Leydig's cells of young pigs (rows 1 and 2) and of green monkeys (rows 3 and 4) are implanted. Rows 1 and 3 show control results (cells are introduced subcutaneously, rows 2 and 4 show experimental results (introducing cells into a formed polyacrylamide capsule).

The present invention is directed to overcoming the above-indicated problems. The authors of the present invention unexpectedly discovered that long-time maintaining the viability of transplanted cells, including heterogeneous ones, in the recipient's organism can be provided by using a polyacrylamide gel capsule being formed in vivo in the organism of a mammal (including a human) in need of therapy with such cells.

So, one of the aspects of the present invention is the use of a polyacrylamide gel for preparing in the organism of a mammal a polyacrylamide capsule formed therein in vivo, which capsule can later be used for cultivating cells transplanted therein.

Unexpectedly to the authors of the present invention, cells injected into the above-
5 said capsule proved to be capable of preserving viability for a long period of time (to 100 days and more) and of producing compounds necessary for the treatment.

Another aspect of the invention is, therefore, a method of cultivating cells necessary for the treatment in the organism of a patient in need of such treatment. The cultivation of cells is preceded by the injection of a polyacrylamide gel into the organism
10 of a mammal; by the formation of a gel capsule during a definite period of time in the organism of a mammal; and by the injection into said capsule of a required amount of cells to be transplanted.

Long-time survival of the cells in the cultivation thereof inside the patient's body proves to be useful for the treatment of a number of diseases, which requires
15 transplantation of autologous or heterologous cells producing biologically active compounds whose deficiency in the organism aggravates or initiates the disease.

The third aspect of the present invention is a method of treating diseases for which immunization with an antigen is indicated, this antigen under usual conditions requiring intensive immunosuppressive therapy.

20 The next aspect of the invention is a method of treating diabetes mellitus, predominantly insulin-dependent one, consisting in that an effective amount of pancreatic β -cells is introduced into a polyacrylamide gel capsule preformed in the organism of a patient.

One more aspect of the present invention is a method of cultivation and
25 modification of heterogeneous cells (tumor cells, Leydig's cells, etc.) in the organism of a mammal with a view to their subsequent use for producing a vaccine preparation. The definition "modification of heterogeneous cells" should be understood as lowering the proliferative activity and immunizing action on the organism.

The invention will further be disclosed in detail by examples of its preferred
30 embodiment, these examples being given by way of illustration only and should not be used for limiting the scope of claims. A person skilled in the art may find a considerable number of possibilities for complementing or modifying the invention which will preserve the above-indicated advantages and will be encompassed by the set of claims.

In a general form the invention is carried out as follows.

A connective-tissue capsule according to the present invention may be formed, for instance, by way of subcutaneous injection of a polyacrylamide gel (PAAG) (in a volume of 1.0—5 ml) to animals, e.g., to Vistar-line rats (in a volume of 1.0—3 ml) or (in a volume of 0.5—1 ml) to mice of C57BLACK and BALB/C lines or to a mammal such as a human (in a volume of 1.0—3.0 ml). Individuals of different sexes may participate in the experiment. Leydig's cells of pubescent young pigs, rats, and green monkeys or tumor cells can be introduced into the gel capsule. Animals to which cells are injected subcutaneously serve as control.

A suspension of viable Leydig's cells from the testicles of pubescent young pigs, rats, and green monkeys is prepared by using solutions containing a nutrient substrate for cells, in particular, compositions of standard Eagle's medium, medium 199, Hanks' solution, etc.

The essence of the proposed method of treating patients suffering from diabetes mellitus is the long-time existence of and production of insulin by pancreatic β -cells of the donor in the recipient's organism, this being achieved by preliminary subcutaneous injection of a polyacrylamide gel to the patient and subsequent transplantation of β -cells into the formed capsule.

The material for the transplantation of β -cells is obtained from the pancreas of mammals (newborn pigs, rabbits, pubescent green monkeys). Cultivation is carried out using standard media and solutions. For preserving β -cells in the active state, a method of sparing enzymatic treatment of the pancreas is employed, which consists in alternating contacts of the tissue with the enzyme and the nutrient medium. As a result of the treatment steps, fragments of the pancreas tissue and β -cells are introduced into cultivation vessels without centrifugation. Disaggregation of the tissue is carried out with a 0.1—0.25% solution of trypsin and chenopsin in different sequences, depending on the donor material. The enzymatic treatment of the tissue is completed during its contacts with the medium, using a "Biotech-m" flask, which provides for controlled stirring of the suspension on a magnetic table.

The resulting cell material is injected to the patient into the connective-tissue capsule which is formed by the polyacrylamide gel preliminarily administered subcutaneously. The amount of the cells depends on the gravity of the recipient's disease.

The Examples which follow illustrate carrying the invention into effect

Example 1

5 A culture of Leydig's cells of newborn pigs in the volume of 0.5 ml with the concentration of cells of 5 million per ml is injected into a polyacrylamide gel capsule to females of Vistar-line rats.

To the control group of animals of the same line, sex and anthropological data a culture of Leydig's cells of newborn pigs is administered subcutaneously. Before injecting the cell culture, the content of testosterone in the blood serum of the animals is measured. Subsequent measurements of testosterone in the blood serum are carried out with different
10 intervals during 7 months in the control and experimental animals simultaneously.

The number of animals in control and in the experiment was 2 individuals in each. Fig. 1 (rows 1 and 2, respectively).

Example 2

15 A culture of Leydig's cells of pubescent green monkeys in the volume of 0.5 ml with the concentration of cells of 5 million per ml is injected into a polyacrylamide gel capsule to females of Vistar-line rats.

To the control group of animals of the same line, sex and anthropological data a culture of Leydig's cells of pubescent green monkeys is administered subcutaneously. Before injecting the cell culture, the content of testosterone in the blood serum of the
20 animals is measured. Subsequent measurements of testosterone in the blood serum are carried out with different intervals during 7 months in the control and experimental animals simultaneously.

The number of animals in control and in the experiment was 2 individuals in each. Fig. 1 (rows 1 and 2, respectively).

25 After 7 months of observations the animals are sacrificed and a histological investigation is carried out. It indicates the presence of a large amount of viable Leydig's cells, so that a conclusion can be drawn about the possibility of vital activity of xeno- and heterogeneous cells in the recipient's organism with the use of a gel.

Example 3

30 PAAG in the volume of 0.5 ml is administered subcutaneously to an experimental group of mice of the BALB/C line (6 individuals). Tumor cells of murine melanoma B-16 are injected into the gel in the volume of 1 ml with the concentration of cells of 1 million cells per ml. Cells of murine melanoma B-16 in the volume of 1 ml with the concentration

of cells of 1 million per ml are administered subcutaneously to a control group of mice of the BALB/C line (6 individuals).

It is known that in mice of the BALB/C line the tumor of murine melanoma B-16 does not grow. In the control group of the animals the tumor growth was found in none of the 6 individuals. In the experimental group of the animals, by way of palpatory examination, a growth of tumor in the PAAG was noted in all the 6 individuals. By the 60th day the experimental animals with the murine melanoma B-16 in the gel are sacrificed. The gel with tumor cells is extracted under aseptic conditions and transferred to a monolayer culture on the nutrient medium RPMI-1640 with 10% fetal serum. Fragments of the capsule with the tumor cells are fixed in a neutral solution of formalin, and a histological investigation is carried out, which allows one to judge about a higher differentiation of melanoma cells and the loss of the proliferative activity by them (Table 1 [1—2]).

TABLE 1. COMPARISON OF THE GROWTH OF MELANOMAS B-16 (MURINE) AND SKMEL 28 (HUMAN) IN MICE OF BALB/C AND C57BLACK LINES

LINE OF MICE	TUMOR STRAIN	GROWTH OF MELANOMA	SPAN OF LIFE	META-STASES
BALB/C + GEL	B-16	+	60 DAYS (observa-tion period)*	-
BALB/C	B-16	-	> OBSERVA-TION PERIOD	-
C57BLACK + GEL	SKMEL28	+	> OBSERVA-TION PERIOD	-
C57BLACK	SKMEL28	-	> OBSERVA-TION PERIOD**	-

* Animals with tumors grown in the gel are sacrificed. The tumor cells isolated from them are used in the next experiment (Table 2).

** Mice are used further in the experiment for estimating immunity against melanoma B-16 (Table 3).

Example 4

A culture of cells prepared as in Example 1 is administered subcutaneously in the amount of 1 ml with the concentration of cells of 1 million to mice of the C57BLACK line (6 individuals).

5 It is known that in mice of the C57BLACK line the tumor of murine melanoma B-16 grows in 100% of cases, death of the animals occurs on the 20—25th day in 100% of cases.

To the control group of C57BLACK mice a culture of cells of murine melanoma B-16 is administered in the amount of 1 ml with the concentration of cells of 1 million.

10 In experimental mice the appearance of symptoms of tumor growth is noted in 60—65 days; in control mice, in 20—23 days

(Table 2).

TABLE 2. TUMORIGENIC ACTIVITY OF MELANOMA B-16, CULTIVATED IN A GEL CAPSULE, IN MICE OF BALB/C LINE, GRAFTED TO MICE OF C57BLACK LINE

No.	TUMOR STRAIN	TIME OF TUMOR APPEARANCE	LIFE-SPAN OF MICE	PRESENCE OF METASTASES
1	Melanoma from gel of mice of BALB/C line (B-16-X)	30 DAYS	60 DAYS	+
2	B-16 (control)	7 DAYS	22 DAYS	+

Example 5

20 PAAG in the volume of 0.5 ml is injected subcutaneously to mice of the C57BLACK line (6 individuals). A cell culture of human melanoma SKMEL is injected into the gel in the amount of 1 ml with the concentration of cells of 1 million.

The control group of mice of the same line (6 individuals) is administered subcutaneously a cell culture of human melanoma SKMEL28 in the volume of 1 ml with the concentration of cells of 1 million.

25 It is known that the cell culture of human melanoma does not grow in mice in 100% of cases. In the experimental group of animals the tumor growth in the gel is determined by palpation on the 15-20th day after the injection. In the control animals no tumor growth is found (Table 1 [3—4]).

Example 6

The group of experimental animals (6 individuals), described in Example 3, is administered subcutaneously a cell culture of murine melanoma B-16 in the volume of 1 ml with the concentration of cells of 1 million. The control group of mice of the C57BLACK line (6 individuals) is administered subcutaneously a cell culture of murine melanoma B-16 in the volume of 1 ml with the concentration of cells of 1 million.

In the control animals subcutaneous melanomas approximately 3—5 cm in diameter develop on the 7—15th day. In the experimental animals no symptoms of tumor are detected during the same period of time (Table 3).

TABLE 3. IMMUNOGENIC ACTIVITY OF HUMAN MELANOMA SKMEL28 FOR MICE

No.	TUMOR STRAIN	TUMOR APPEARANCE TIME	DEATH OF ANIMALS
5	B-16	-	> 60 DAYS
6	B-16	7—15 DAYS	18—20 DAYS

So, the results presented hereinabove give grounds to believe that the method of cultivating heterogeneous cells in PAAG in vivo, whereby the proliferative activity of tumor cells lowers and the cultivated cells produce an immunizing effect on the organism, can be used for vaccination and vaccinothrapy.

Example 7

Female patient F., aged 37. Insulin-dependent diabetes mellitus was diagnosed 11 years ago, one year after the parturition. The pregnancy was aggravated by toxicosis during the second half of the pregnancy period, by nephropathology, a considerable, to 26 kg, gain in weight. The character of the disease has been unstable all these years, and considerable efforts were required in choosing adequate insulin therapy. The use of exogenous insulin was varied from 58 units per day to 30 units per day. During the last two years pathological changes in the kidneys were diagnosed, defined as diabetic nephropathy. In urinalyses a 10—12-fold increase of the upper boundary of proteinuria is noted. The arterial pressure increases to 170/110 mm Hg.

A culture of pancreatic cells of newborn rabbits was administered to the patient subcutaneously, by injecting the culture into a preliminarily formed capsule. Already 7 days later the patient noted an improvement in the general condition, a reduction of the

sensation of thirst and dryness of the mucous membrane of the oral cavity, lowering of the arterial pressure down to 140/90 mm Hg. In 15 days the condition of the patient was such that the need in exogenous insulin could be lowered from 30 units to 18 units (blood and urine control). In 30 days the need in exogenous insulin lowered to 12 units per day, and
5 towards the close of the 2nd month, to 4 units per day.

The patient's condition has been followed-up during 12 months. No clinical manifestations of nephropathy are detected, the arterial pressure is within the age norm. The patient was transferred to oral taking of anti-diabetic preparations with obligatory observance of diabetic diet and control of glucose in blood, in urine, as well as of
10 glycosylated hemoglobin.

Example 8

Male patient K., aged 52. Insulin-dependent diabetes mellitus was diagnosed since the age of 18 against the background of a strong stress situation. At first the character of the disease was unstably severe. The doses of exogenous insulin reached 70 units per day.
15 In recent years the course of the disease has stabilized, but worsening of the state occurred after stress situations and errors in the diet.

During the last three years worsening of the state of the vessels of the lower extremities, lowering of the libido, worsening of the erection and deterioration of the coitus quality were observed. Diabetic angiopathy of the lower extremities and penis was
20 diagnosed. During the last year the need in exogenous insulin was from 20 units per day to 40 units per day.

The patient was administered with a culture of pancreatic cells of 14-days' pigs, injected into a preliminarily formed capsule. Two weeks later the patient noted a improvement in the general condition. In one month the need in exogenous insulin lowered
25 to 12 units per day. In 2 months this need lowered to 6 units per day. Four months after the transplantation the patient was transferred to oral taking of anti-diabetic preparations. The sexual life of the patient normalized, the condition of the vessels of the lower extremities improved appreciably.

The subjective and objective symptoms of examined patients, the data of additional
30 methods of blood and urine investigation allow one to speak of a high effectiveness of this method of treating diabetes mellitus, this leading to substantial reduction of the doses of exogenous insulin taken by the patients, and in some cases even to refusal of insulin therapy. The method does not require immunosuppressive therapy, lowers the risk of

secondary complications of diabetes mellitus: rethino-, neuro-, nephropathies. The method makes it possible to improve appreciably the quality of life of patients. As a rule, the therapeutic effect lasts for 10—20 months, depending on the severity of the disease.

5 The amount of cells to be transplanted also depends on the severity of the course of diabetes mellitus, particularly on the quantity of exogenous insulin taken by the patient.

10 The proposed invention makes it possible, using "a polyacrylamide gel", by introducing it into the organism of a mammal, to form in vivo a capsule, which later on, being injected with viable cells for transplantation, functions as a chamber for cultivating producer cells during a long period of time, required for treating with a compound produced by the cell, when said compound, releasing from this artificially formed chamber, produces the desired effect on the organism of a patient. The use of a polyacrylamide gel for the indicated purposes allows maintaining the viability of cultivated cells for a long time and thereby provides a prolonged curative effect. Said use makes it possible to rule out immunosuppressive therapy and may find very extensive application in
15 practical medicine.

TOP SECRET 96406860

CLAIMS

1. The use of a polyacrylamide gel for forming a capsule in the tissue of the organism of a mammal, said capsule being intended for cultivating transplanted autologous or xenogenous cells of an animal for a long period of time, said transplanted cells being intended for producing a biologically active component, the absence or deficiency of which in the organism induces a disease, and/or an increase in the content of which in the organism contributes to improving the condition of the organism suffering from a pathology.

2. The use according to claim 1, wherein said organism is a human organism.

3. The use according to claim 2, wherein said pathology is diabetes mellitus.

4. The use according to claims 1—3, wherein said transplanted cells are pancreatic β -cells.

5. The use according to claim 4, wherein said pancreatic cells are cells of newborn rabbits or cells of young pigs.

6. A method of cultivating and modifying heterogeneous cells of mammals, with subsequent use of said cells for producing vaccine preparations, wherein cultivating heterogeneous cells is carried out during a long period of time in a living organism by preliminary administration a polyacrylamide gel to a mammal, followed by injecting heterogeneous or autogenous cells of mammals into said gel.

7. A method according to claim 6, wherein tumor cells are used as said heterogeneous cells.

8. A method according to claim 6, wherein Leydig's cells are used as said heterogeneous cells.

9. A method according to any one of claims 6—9, wherein said modification of cells consists in lowering their proliferative activity and in the immunizing effect on the organism.

10. A method of treating diabetes mellitus by the method of transplanting pancreatic β -cells, wherein the recipient is preliminarily administered a polyacrylamide gel, followed by transplanting a therapeutically significant amount of pancreatic β -cells into said gel.

11. A method according to claim 10, wherein said β -cells are cells of newborn rabbits or cells of young pigs.

ABSTRACT

The invention relates to the field of medicine and more particularly it relates to the problem of vaccination against tumor cells and vaccinothrapy of oncological diseases, and also to a method of treating diabetes mellitus. In the invention a new method of cultivating
5 cells is proposed, which contemplates forming a capsule of a polyacrylamide gel in the tissue of an animal, including a human, into which capsule desirable cells are injected. The invention provides for maintaining the viability of cells during a long period of time.

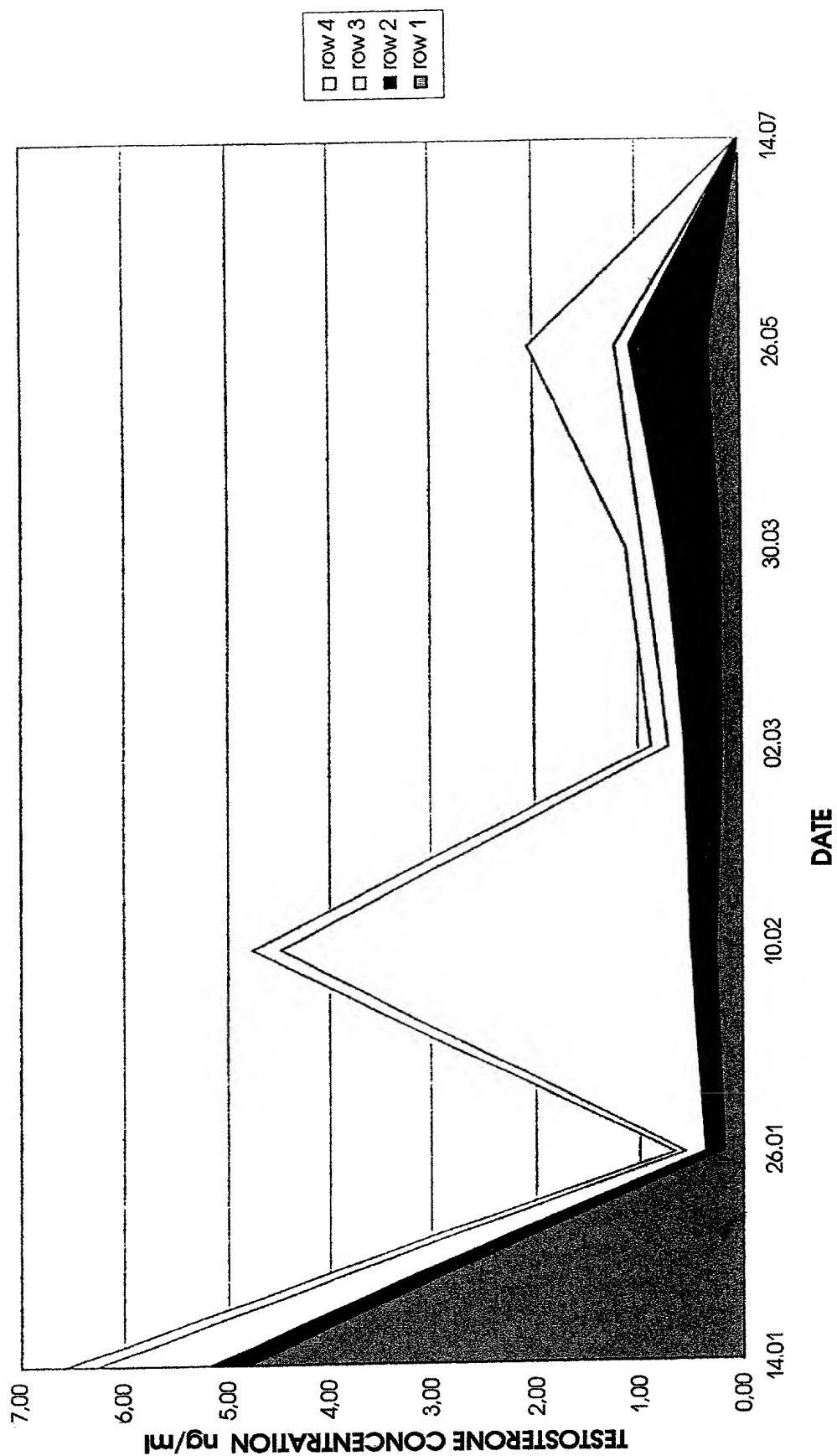


FIG. 1

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL,
CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

☐ original.

☐ design.

NOTE: *With the exception of a supplemental oath or declaration submitted in a reissue, a supplemental oath or declaration is not treated as an amendment under 37 CFR 1.312 (Amendments after allowance). M.P.E.P. Section 714.16, 7th Ed.*

☐ supplemental.

NOTE: *If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items.*

☒ national stage of PCT.

NOTE: *If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P.*

NOTE: *See 37 C.F.R. Section 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.*

☐ divisional.

☐ continuation.

NOTE: *Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C.F.R. Section 1.53(b) (application filing requirements-nonprovisional application).*

☐ continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: *If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.*

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

107620 96406860

TITLE OF INVENTION

Use of Polyacrylamide Gel for Forming a Capsule in the Tissue of the Organism of a Mammal, a Method of Cultivating Cells, and a Method of Treating Oncological Diseases and Diabetes Mellitus

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) ☒ is attached hereto.

NOTE: "The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60).

(b) ☐ was filed on _____, ☐ as Application No. _____
☐ and was amended on _____ (if applicable).

NOTE: Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 C.F.R. Section 1.67.

NOTE: "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:

(A) application number (consisting of the series code and the serial number, e.g., 08/123,456);

(B) serial number and filing date;

(C) attorney docket number which was on the specification as filed;

(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or

(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.

M.P.E.P. Section 601.01(a), 7th ed.

- (c) ☒ was described and claimed in PCT International Application No. PCT/RU00/00477 filed
on Nov. 22, and as amended under PCT Article 19 on _____ (if any).
2000

SUPPLEMENTAL DECLARATION (37 C.F.R. Section 1.67(b))

(complete the following where a supplemental declaration is being submitted)

- ☐ I hereby declare that the subject matter of the
- ☐ attached amendment
- ☐ amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application,
above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified
specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in
37, Code of Federal Regulations, Section 1.56,

(also check the following items, if desired)

- ☐ and which is material to the examination of this application, namely, information where
there is a substantial likelihood that a reasonable Examiner would consider it important
in deciding whether to allow the application to issue as a patent, and
- ☐ in compliance with this duty, there is attached an information disclosure
statement, in accordance with 37 C.F.R. Section 1.98.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declaration as required by Section 1.63. The claim for priority and the certified copy of the foreign application specified in 35 U.S.C. Section 119(b) must be filed in the case of an interference (Section 1.630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted. If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in Section 1.17(i). If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner; or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 C.F.R. Section 1.55(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

- (d) ☐ no such applications have been filed. .
(e) ☒ such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U.S. itself claimed priority check item (e), enter the details below and make the priority claim.

**PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION
AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)**

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, MONTH, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
RU	99125349	08/12/1999	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
RU	2000116208	23/06/2000	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. Section 119(e))

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER

FILING DATE

_____/_____
_____/_____
_____/_____

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)
UNDER 35 U.S.C. SECTION 120

[] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

NOTE: If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. Section 120.

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179

RICHARD P. BERG, 28145

JOHN RICHARDS, 31053

JULIAN H. COHEN, 20302

RICHARD J. STREIT, 25765

WILLIAM R. EVANS 25858

PETER D. GALLOWAY, 27885

JANET I. CORD, 33778

IAN C. BAILLIE, 24090

CLIFFORD J. MASS, 30086

THOMAS F. PETERSON, 24790

CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

- [] I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.
- [] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

NOTE: "Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4)." Section 601.03, M.P.E.P., 7th Ed.

SEND CORRESPONDENCE TO

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

(complete the following if applicable)

Since this filing is a [] continuation [] divisional there is attached hereto a Change of Correspondence Address so that there will be no question as to where the PTO should direct all correspondence.

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

NOTE: Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R. Section 1.63(a)(3).

NOTE: Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors. Section 1.63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor. 62 Fed. Reg. 53,131, 53,142, October 10, 1997,

Full name of sole or first inventor

100
Dmitry Vladimirovich ZYBIN
(Given Name) (Middle Initial or Name) Family (Or Last Name)
Inventor's signature Дмитрий Владимирович Зыбин
Date July 23, 2001 Country of Citizenship Russian Federation
Residence Russian Federation, Moscow RUS
Post Office Address Russian Federation, Moscow, ulitsa Armavirskaya,
5, kv. 212

Full name of second joint inventor, if any

200
Alexei Gennadievich KOTELEVITS
(Given Name) (Middle Initial or Name) Family (Or Last Name)
Inventor's signature Алексей Геннадьевич Котелевич
Date July 23, 2001 Country of Citizenship Russian Federation
Residence Russian Federation, Moscow RUS
Post Office Address Russian Federation, Moscow, ulitsa Pyatnitskaya,
39, kv.1

Full name of third joint inventor, if any

300
Sergei Evgenievich SEVERIN
(Given Name) (Middle Initial or Name) Family (Or Last Name)
Inventor's signature Сергей Евгеньевич Северин
Date July 23, 2001 Country of Citizenship Russian Federation
Residence Russian Federation, Moscow RUS
Post Office Address Russian Federation, Moscow, Novye Cheremushki,
kvartal 24-25, korp. 8B, kv.245

(check proper box(es) for any of the following added page(s)
that form a part of this declaration)

☒ **Signature** for fourth and subsequent joint inventors. *Number of pages added* 1

* * *

☐ **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

☐ **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. Section 1.47. *Number of pages added* _____

* * *

☐ Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. Section 1.47)

* * *

☐ Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

☐ Number of pages added _____

* * *

☐ Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration,
then end this Declaration with this page and check the following item)

☐ This declaration ends with this page.

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

NOTE: Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R. Section 1.63(a)(3).

NOTE: Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors. Section 1.63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor. 62 Fed. Reg. 53,131, 53,142, October 10, 1997.

Full name of the forth inventor

4-00 Vladimir Konstantinovich SOLOGUB
(Given Name) (Middle Initial or Name) Family (Or Last Name)

Inventor's signature Владимир Константинович Сологуб

Date July 23, 2001 Country of Citizenship Russian Federation

Residence Russian Federation, Moscow RUX

Post Office Address Russian Federation, Moscow, ulitsa Garibaldi,
10, korp. 3, kv.304

Full name of: the fifth inventor

5-00 Ljubov Leonidovna MIRONOVA
(Given Name) (Middle Initial or Name) Family (Or Last Name)

Inventor's signature Любовь Леонидовна Мирнова

Date July 23, 2001 Country of Citizenship Russian Federation

Residence Russian Federation, Moskovskaya oblast RUX

Post Office Address Russian Federation, Moskovskaya oblast, Leninsky
raion, pos. "Institut polimelita", 1, kv.7

Full name of

(Given Name) (Middle Initial or Name) Family (Or Last Name)

Inventor's signature

Date Country of Citizenship

Residence

Post Office Address